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09/831,426	05/08/2001	Florence Bordon-Pallier	146.1364	4261

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EXAMINER
YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
1642	

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24

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,426	BORDON-PALLIER ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-14,17 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-14,17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Sequence Alignment

DETAILED ACTION

1. As outlined in the petition decision mailed 12/5/2003 (paper no.23), groups I-VII are rejoined and examined on the merits.

2. The amendment filed 8/28/2003 (paper no. 22) is acknowledged and entered into the record. Accordingly, claims 1, 15 and 16 are canceled without prejudice or disclaimer, claims 2-14 and 17-18 are pending and examined on the record.

Information Disclosure Statement

3. The Information Disclosure Statement filed 4/30/2003 (paper no. 20) is acknowledged and considered. A signed copy of the IDS is attached hereto.

Claim Rejections Maintained - 35 USC § 112, 1st paragraph

4. The rejection of claims 17 and 18 under 35 USC 112, 1st paragraph as lacking an enabling disclosure is maintained for the reasons of record. Applicant argues that the instant specification provides the skilled artisan with an enabling disclosure so as to be able to practice the instant invention without undue experimentation. Applicant further furnishes a reference stating that at the time the invention was field the skilled artisan would be able to correlate the findings of Tanabe *et al* to the instant invention so as be enabled to practice the instant invention. Applicant's arguments have been carefully considered but are not deemed persuasive. As stated in the prior office action, the specification has not provided the skilled artisan with any indication that the administration of recombinant DNA to a subject would indeed treat a disease associated

with transcriptional regulation, let alone the treatment of cancer. As indicated in the prior office action, cancer is a rather unpredictable disease to treat and the instant invention is essentially the application of a gene therapy method. One skilled in the art cannot extrapolate the teachings of the specification to the scope of the claims because the specification provides no exemplification of or guidance on how to use the claimed recombinat DNA for the treatment of any disease associated with transcriptional regulation with any predictability. Gene therapy against tumors is highly unpredictable as underscored by Crystal, R.G. (Science, Vol. 270, October 1995, pages 404-410) who teaches that in tumor vaccine studies intended to evoke a tumor-directed immune response, there is no convicining evidence (other than anecdotal case reports) that tumors actually regress, despite the promising observations in experimental animals. In other words, humans are not simply large mice (page 409, 1st column). More recently, Tait *et al.* (Clin.Canc.Res., Vol. 5, July 1999, pages 1708-1714) revealed just how unpredictable gene therapy was in the clinical setting. The authors' prior phase I trial of 12 patients with extensive ovarian cancer treated with a retroviral vector expressing the BRCA1 splice variant (LXSN-BRCA1sv) demonsrated vector stability, minimal immune response, gene transfer and expression, and some tumor reduction in the patients (page 1708, 2nd column, 2nd paragraph). In contrast, the Phase II trial inititiated in pateints with stage III and IV grade ovarian cancer, showed a high preponderance for vector instability (vector was degraded rapidly), a rapid immunological response invoking neutralizing antibodies to the retroviral vector, and no clinical response to the therapy. Although the difference in response to the therapy may be attributed to

differences in immunocompetence between the phase I and II patients (page 1712, 2nd column), the end result seems to indicate that further experimentation is necessary prior to the successful application of DNA vaccines, especially with the regards to cancer therapy. Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

Therefore, given the teachings of unpredictability associated with both gene therapy and cancer and the lack of working examples in a highly unpredictable field such as cancer, the specification has essentially forced the skilled artisan to experiment in order to practice the invention.

New Arguments

Claim Rejections - 35 USC § 112, 2nd paragraph

5. Claims 2-13, 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 2 and dependent claims thereof are indefinite in the recitation of the phrase "according to claim 1" because the phrase refers to a canceled claim.

7. Claim 9 is indefinite for the recitation of the term "AA", because the term has not been associated with an adequate definition in the specification. For the purposes of examination, the term "AA" will be interpreted as shorthand for "amino acid".

Claim Rejections - 35 USC § 112, 1st paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 6-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case has only set forth the nucleotide sequence and amino acid sequence of hTFIIIA which are represented by SEQ ID No: 3 and 4 and SEQ ID No: 2, respectively. Therefore, the

written description in this case is not commensurate in scope to claims that read on homologues, variants, derivatives, or analogues of SEQ ID Nos: 2-4.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

What are allelic variants? Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined, nor in this case, is the structure of allelic variant proteins encoded by allelic variant genes defined. With the exception of SEQ ID Nos: 2-4, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and or the encoded amino acid variants and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid and

amino acid sequences themselves are required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Although these court findings are drawn to DNA art, the findings are clearly applicable to the claimed proteins.

Furthermore, although drawn specifically drawn to the DNA art the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly applicable to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Support for allelic variants, homologues and derivatives are provided in the specification on pages 6-7. However, no disclosure, beyond the mere mention of allelic variants, homologues or derivatives is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645. The Guidelines for the Examination of Patent Applications Under the 35

U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Applicant does not appear to have reduced to practice any variants, homologues, derivatives, or analogues of any sequences represented by SEQ ID Nos: 2-4 . Neither has Applicant provided a sufficient written description of any structure that may be correlated with the desired transcriptional activity. The genus of analogues, derivatives, homologues or analogues compounds encompassed by this term is extensive and the artisan would not be able to recognize that Applicant was in possession of the invention as now claimed. Consequently, Applicant was not in possession of the instant claimed invention.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

Therefore only an isolated nucleic acid of SEQ ID No: 3-4 and the amino acid sequence of SEQ ID No: 2 meets the written description provision of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 112, 1st paragraph

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 14 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 14 recite a specific plasmid.

It is apparent that the recited plasmid is required to practice the claimed invention, because they are specifically required in the claims. As required elements they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the plasmid listed in claim 14. See 37 CFR 1.802.

The specification does not provide a repeatable method for obtaining the plasmid of claim 14, and they do not appear to be readily available material. Deposit of the cell lines that harbors said plasmid would satisfy the enablement requirements of 35 U.S.C. 112. While the specification states on page 14 that the plasmid is deposited at the CNCM under the number I-2071, the specification does not indicate the terms of the deposit.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

Claim Rejections - 35 USC § 102

12. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

13. Claims 2-4,6-9,17 and 18 rejected under 35 U.S.C. 102(b) as being anticipated by Fujikawa *et al* (EP 0704526A1, previously cited). Claims are drawn to a recombinant DNA sequence comprising the hTFIIIA gene coding for amino acid sequence SEQ ID No: 2 (claim 2), wherein the DNA sequence contains the sequence of SEQ ID No: 3 (claim 3) or SEQ ID No: 4 (claim 4). The claims are further limited to DNA sequence which hybridizes to the DNA sequence of claim 2 and proteins that have significant homology to SEQ ID No: 2 (claim 6); DNA sequences that have modifications introduced by suppression, insertion or substitution (claim 7); DNA sequences that are 50-70% identical to that of the DNA sequence of claim 2 (claim 8); DNA sequences which code for amino acids sequences which are at lest 40% identical to the DNA encoding the protein of SEQ ID No: 2 (claim 9); methods of treating a disease linked to

transcription control disorders comprising the administration of the DNA or protein of claim 2 (claim 17), wherein the disease is cancer (claim 18).

Fujikawa *et al* disclose a nucleic acid sequence that encodes a protein that contains the sequence of SEQ ID No: 2, wherein the DNA sequence disclosed by Fujikawa *et al* contains the sequence of SEQ ID No: 3 and 4. Because the sequence taught by Fujikawa *et al* is 99.4% homologous to that of SEQ ID No: 3 and 4 in the absence of evidence to the contrary, the sequence taught by Fujikawa *et al* would hybridize to SEQ ID Nos: 3 and 4. Furthermore, because there is a high degree of similarity between the sequence of Fujikawa *et al* (i.e. 99.3%) and that of the instantly claimed invention, DNA sequences that have modifications fall within the scope of that taught by Fujikawa *et al*. Moreover, Fujikawa *et al* discloses that the DNA sequences are useful in the treatment of diseases especially cancer (see page 2 and claims 1-9).

Claim Rejections - 35 USC § 102

14. Claims 2-4 and 6-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Arakawa *et al* (Cytogenet Cell Genet 1995;70(3-4):235-8, previously cited). Claims are drawn to a recombinant DNA sequence comprising the hTFIIIA gene coding for amino acid sequence SEQ ID No: 2 (claim 2), wherein the DNA sequence contains the sequence of SEQ ID No: 3 (claim 3) or SEQ ID No: 4 (claim 4). The claims are further limited to DNA sequence which hybridizes to the DNA sequence of claim 2 and proteins that have significant homology to SEQ ID No: 2 (claim 6); DNA sequences that have modifications introduced by suppression, insertion or substitution (claim 7); DNA

sequences that are 50-70% identical to that of the DNA sequence of claim 2 (claim 8); DNA sequences which code for amino acids sequences which are at lest 40% identical to the DNA encoding the protein of SEQ ID No: 2 (claim 9).

Arakawa *et al* disclose a nucleic acid sequence that encodes a protein that contains the sequence of SEQ ID No: 2, wherein the DNA sequence disclosed by Arakawa *et al* contains the sequence of SEQ ID No: 3 and 4. Because the sequence taught by Arakawa *et al* is 99.4% homologous to that of SEQ ID No: 3 and 4 in the absence of evidence to the contrary, the sequence taught by Arakawa *et al* would hybridize to SEQ ID Nos: 3 and 4. Furthermore, because there is a high degree of similarity between the sequence of Arakawa *et al* (i.e. 99.3%) and that of the instantly claimed invention, DNA sequences that have modifications fall within the scope of that taught by Arakawa *et al*.

Conclusion

15. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B Nickol for:

Christopher Yaen
Art Unit 1642
January 6, 2004